1. What, in your opinion, is the single largest trend with respect to solubility/solubility technology?

CS: In my opinion there is not one single trend in solubility technology. As we have answered the “simple questions” on solubility measurements getting more data on solubility using generic, technical high- or mid-throughput approaches in recent years, now the more individual questions gain importance.

At the end of the day, solubility itself will not be the final goal to reach in pharmaceutical research and development: Solubility represents only a single parameter – nevertheless an important one – in realizing adequate bioavailability. As solubility is much easier and faster to measure compared to bioavailability, improvement of methods including automation to measure solubility has been a major task during the last decade.

Now that these technical improvements have been made in the lab in recent years, today what is becoming more and more important for oral solid dosage forms are the questions:

• How will solubility translate into bioavailability?
• What role does dissolution rate play in bioavailability?

To answer these – especially during earlier phases of research and development (e.g. lead optimization in medicinal chemistry) - a whole set of new technologies is currently on the way. They include:

• Tools to measure intrinsic or apparent dissolution rates using lower mg amounts of a research compound.
• Tools to characterize particle properties such as particle size and crystalline form which will influence dissolution rate also on a small scale.
• In-silico tools to predict pharmacokinetics based on physical-chemical properties to get a rough understanding of the bioavailability of a research compound and the parameters which will be critical in guaranteeing adequate bioavailability. In principle, this is nothing else but an improvement of the classical BCS (biopharmaceutical classification scheme) scheme or a more mechanistic approach to developing IVIVC (in-vitro in-vivo correlation).

As it turns out for many research compounds that techniques have to be used which will realize dissolved states of a compound which are oversaturated referred to the thermodynamically stable crystalline form of a compound, also methods to characterize such metastable systems are moving more and more into focus. To get a better understanding of the reliability and risks of such “spring and parachute” approaches (e.g. nano-milling, co-crystals, hot-melt extrudates, molecular dispere solutions, amorphous active pharmaceutical ingredients and even more traditional ones such as pharmaceutical salts), there will be a greater need for methods answering these questions in a more compound- and formulation-specific way. This road leads away from the generic “one-fits-all approach”, at least for compounds moving from research towards clinical development.
High throughput screening allows scientists the opportunity to collect and evaluate more data, thus the scientist is able to evaluate a broader range of solubilizing technologies at lower cost and with less API. While formulations of solid dispersions have been known since the 1960s to improve API bioavailability, the technology has received much greater attention recently as a way to address the development challenges of the increasing number of poorly soluble APIs. The adoption and commercial scale use of melt extrusion as a process technology have directed new energy toward solid dispersion technology. As melt extrusion is a continuous process, it is a cost efficient system for forming solid dispersions. For compounds with thermostability issues or with an extremely high melting point, spray drying may be a more suitable process for achieving a solid dispersion. Hot melt extrusion and spray drying should be considered as complementary process technologies for solid dispersions with advantages and limitations to each.

As a consequence of increasing utilization of combinatorial and high throughput chemistry throughout the last two decades the pharmaceutical industry has found itself increasingly trying to develop new ‘non-druggable’ new chemical entities (NCEs) 1. These candidates typically have high molecular weights (MWs) and lipophilicities (cLogP) and commensurately low aqueous solubilities (often < 10 µg/ml). This often translates into poor exposure, poor metabolic clearance and poor toxicity (based on an increased likelihood of binding to multiple pharmacological targets). Lipinski’s Rule of 5 2 was formulated to provide guidance to medicinal chemists to try and optimize those factors that were key in increasing aqueous solubility and permeability (‘druggability’ aligned). Unfortunately, lipophilic compounds still tend to be progressed as they perform better in early discovery screens. However, there are now many ongoing initiatives across the whole industry aimed at trying to reduce cLogP (and commensurately MW and aromaticity) of future compound libraries, with the ultimate aim of increasing aqueous solubility.

2. How has the landscape of solubility shifted since inception, including the arrival of the Biopharmaceutics Classification System?

As people recognized that solubility (or lack of) of research compounds became a critical parameter due to the advent of high-throughput screening and combinatorial chemistry, there were two ways in which people reacted:

- Finding rules on how to design research compounds: definitely Lipinski’s “rule of five” represents the most prominent one but this includes also others such as limiting the number of aromatic ring systems or avoiding long aliphatic chains up to in-silico tools to predict solubility. Definitely, good in-silico predictions for solubility are still representing a challenge.
- Implementation of automated methods to measure solubility in higher throughput using a smaller amount of the research compound.

Both represent generic approaches which are intended to deal with large numbers of compounds. Even with these approaches still today we see many late-stage research compounds and development candidates in clinical development exhibiting low solubility. These compounds demand more and more individual care using a much broader set of techniques to improve solubility and to characterize the compounds and formulations. In this context “individual care” represents not only a technical method but also a means to address solubility in an interdisciplinary way. The question has to be addressed by medicinal chemists, people from DMPK departments, formulation people and people dealing with physical-chemical characterization.

The BCS system provides a framework that enables the scientist to tailor formulation development approaches according to the API classification, and to focus resources on development work that may provide the best outcome for the least expenditure. Since the BCS categorizes APIs on both solubility and permeability, there is a need for the scientist to also understand physiological processes that may affect permeability, which is a far more complex area.

The BCS provides clearly defined guidelines for solubility and permeability. By understanding an API’s solubility and permeability, it assists in establishing a development path during the discovery and development. A clear understanding on BCS is also instrumental to the risk assessment of APIs.

Historically, solubility was seen as an ‘absolute’ value defined essentially by the purity of the molecule. However, both kinetic solubility (typically used in drug discovery to support high throughput approaches, and usually in DMSO/aqueous based solvent mixtures) and equilibrium solubility (typically used in drug development and usually in water or bio-relevant media) have been used inter-changeably, which often prompts confusion as to the ‘true’ solubility.

With greater understanding of the solid state came a clearer understanding that it was the crystalline state that defined solubility and hence factors that affected the conformational or packing efficiencies of molecules were influential in affecting solubility. In addition, lipophilicity also has a key role to play in influencing solubility, as per General Solubility Equation:

\[ \log S = -\log P - 0.01 (MP-25) + 0.05 \]

Where S is solubility, P is lipophilicity as measured by octanol/water partitioning, MP is melting point.

Thus, molecular approaches, such as salt formation, co-crystals, polymorphism, and amorphicity (or lack of crystallinity) have all been utilized to improve solubility of NCEs. Lastly, the key role that solubility (and permeability) played in defining the bioavailability of the NCE led to the development of the Biopharmaceutical Classification System (BCS) by Amidon [3] and others. Thus, solubility has evolved from an abstract concept that defined the quality of the compound, to an essential parameter that underpins the potential developability of all orally delivered pharmaceutical molecules.

3. How important is advancing the science and technology of solubility to driving improvements in time-to-market and in reducing drug development costs in general?

This is becoming more important. For poorly soluble compounds, there is a significant risk that the drug delivery system of choice (or “enabling technology”) will not even be evaluated early in the development process, and the pharmaceutical process for pre-clinical or clinical studies has a relatively long iteration time, which would cause delay if the first approaches are not successful. The challenge for industry is to utilize the right enabling technologies early enough in the development process without having to try everything for every molecule.

If a compound is poorly soluble, the development program can be every time and resource consuming. The approaches for addressing solubility need to be understood early in the development process. An
understanding of the physical and chemical properties of the API and excipients is critical to identification of the right development approach, and could lead to a reduction in the development timelines.

At ISP, we are a resource for companies developing poorly soluble compounds. We have developed expertise in spray dried dispersions having worked with over 100 actives while working with all the available pharmaceutically-acceptable polymers. In addition, we have a fundamental understanding of polymer properties and active research programs to build more in-depth understanding of the physicochemical properties and the working mechanisms of polymers. Today, we are actively exploring new approaches to solve challenging solubility problems.

4. What country/region, in your opinion, is currently leading the way in solubility technology and why?

CS: To my notice there is not one region leading in this field. Instead there are many small but important steps which are being taken in quite a lot of different countries.

DE: Physical property inflation, i.e. increasing lipophilicity, MW and aromaticity (leading to reduced solubility) is directly attributable for the current unacceptably high attrition rate. Consequently, there has been much greater emphasis on using in silico modelling to enhance solubility, and this has occurred on a world-wide basis across the whole Industry.

Modelling of the inter-relationships between kinetic solubilities and their lipophilicities of more than 100,000 compounds has been recently undertaken [4]. Building on the relationships described in the General Solubility Equation has led to the derivation of the Solubility Forecast Index (SFI):

\[ SFI = \log D_{ph 7.4} + \text{No. of aromatic rings} \]  

Where \( \log D_{ph 7.4} \) is the calculated distribution coefficient at intestinal pH (7.4); i.e. the effective lipophilicity at pH 7.4

The SFI has been proposed as a simple yet effective means of predicting aqueous solubility.

5. What are some of the most promising new techniques being implemented today to address the challenges of low solubility compounds?

ST: For faster action and/or increased bioavailability, any drug delivery system that provides drug in solution, such as softgel capsules, has a head start on any technology based around particulate or amorphous drug powder. New Vegicaps® capsules allow higher temperatures to be used during filling, that can further increase the amount of API that can be encapsulated, that would normally not be possible due to viscosity constraints.

VB: Although the concept of solid dispersions has existed for some time, and products using the technology are commercially available, we are still advancing our understanding about these systems, as well as working to identify new approaches in the solubilization field. For example, the superdisintegrant Polypasdone® crospovidone has been used as an insoluble carrier using hot melt extrusion to improve drug solubility.

CS: Definitely this is a broad range of technical solubility approaches allowing higher throughput, reduced compound consumption and additional assessment of physical-chemical properties closely linked to solubility. Furthermore, this includes progress in the use of biorelevant media for determination of solubility and in-silico tools to predict pharmacokinetics based on solubility.

DE: The use of in-silico computational methodologies that accurately predict solubility (and permeability) will be absolutely essential if we are to move our existing drug-libraries into a more ‘druggable’ space that facilitate development of more soluble NCEs.

However, a recent challenge: Can you predict solubilities of 32 molecules using a database of 100 reliable measurements? [6], was met with limited success. Over 99 respondents rallied to the challenge, utilizing a wide range of different statistical and computational approaches, but most met with limited success. Only one-fifth of respondents accurately predicted the correct solubilities of the full test set [7].

Despite the wide ranging in silico approaches utilized within the challenge there are still no definitive methods that can accurately predict aqueous solubility. It appears clear that the accuracy of these predictive models is highly dependent on the ability of the reference set to fully cover the chemical space of the test set.

6. What impact are they having already, and how large an impact in the future, will nanoparticle and nanoencapsulation technology have on solubility technology?

ST: For many APIs with solubility constraints, nanoparticulates may seem the obvious first choice which might lead to other enabling technologies being put on hold. However, as with any technology, there may be significant challenges to overcome (such as stabilizing particle size), and if the technology is ultimately unsuccessful, there is a risk of delay if no other approaches are being developed in parallel.

VB: This is a research area that has generated significant academic interest as well as marketed products. The mechanism of these formulations is relatively well understood and proof-of-concept can be easily achieved. However, the patent landscape is crowded and requires review. Such technologies could be extremely useful for poorly soluble compounds intended for intravenous delivery; however, there are still many technical and regulation challenges that need to be addressed before these approaches can be more widely applied.

7. If things progress as they have the past five years, what can we expect in the next five years, with respect to solubility?

CS: For the next five years I would expect that we will get a clearer understanding of which kind of solubility data can be most efficiently used during which phase of pharmaceutical research and development. The same expectation is linked to measuring dissolution rates and assessing precipitation behavior in biorelevant scenarios. Currently the vast majority of measurements of solubility is carried out in simple buffer systems such as buffers described in the pharmacopeias. Nevertheless, as we see that solubility measured in such media does not translate straightforwardly into solubility in biorelevant media – e.g. FaSSIF and FeSSIF – and even not directly into bioavailability in animals and humans, my expectation would be that during the next five years we will get a better idea of which kind of solubility data is useful at which stage of pharmaceutical research and development.
Accordingly, instead of only increasing throughput for solubility measurements, we should focus on implementing less generic and more rational approaches which clearly look for correlations between results from solubility measurements and in-vivo results. This will take into account more and more compound-specific properties by examining, for instance, pH-solubility and dissolution profiles including common-ion effects, investigating effects of surfactants or co-solvents, e.g. bile salts or excipients on solubilization or even taking into account molecules that will form micellar solutions by themselves. Another aspect asking for more compound-specific approaches is based on the fact that we see more and more compounds showing pronounced variability of solubility under biorelevant conditions.

Still another aspect: So far we have mainly dealt with answering questions such as “To what extent does my drug dissolve?” and “How quickly does it dissolve?” Beyond this, what will become more and more important as enabling techniques are increasingly used, will be – in addition to the abovementioned questions – finding answers to the questions “How long will my drug be present in an oversaturated solution?”; “Will it precipitate in the GI-tract?”; “Which parameters will effect precipitation?”; “In which solid state form will it precipitate?”; “Will it redissolve?”; “If yes; how much and how quickly?”.

Obviously, these are questions which have to be addressed in interdisciplinary teams as mentioned above. At this stage hopefully also people from clinical research come into play, as one challenge where solubility clearly plays a key role is posed by food effects of certain drug molecules.

DE: I’m not sure that I see the future evolution as being part of the historical continuum. Rather, we have reached a stage where there is no future in developing more of the same, i.e. essentially non-druggable NCEs. The attrition rate of first time in human (FTIH) candidates across the Industry is just too high (ca. 90%) and consequently we have to implement radical strategies to move away from our existing compound libraries that promulgate development of NCEs with high lipophilicity and commensurately low aqueous solubilities.

ST: It will be really research and development project teams who will benefit from the above-mentioned topics. Assessing and designing appropriate solubility as well as monitoring in-vivo results which are a consequence of solubility are areas calling for a joint effort by project teams ranging from Medicinal Chemistry, DMPK, Pharmaceutical Development, Analytics and finally also from Clinical Development.

In terms of drug properties the most benefit will be realized for drugs which are borderline cases: in the past there have been projects where solubility was not an issue at all, because it was clear that solubility would not represent a bottleneck for absorption of the molecule. At the other extreme, there are research compounds where it becomes – unfortunately – clear that solubility represents a parameter which will prohibit successful clinical development. In many cases the intermediate scenario in between these two extremes is manifested by compounds exhibiting solubility and bioavailability which can be highly variable depending on different in-vitro and in-vivo parameters. For these compounds it will be highly beneficial to get a mechanistic understanding - using approaches described above – of which parameters affecting solubility are critical and how to control them.

VB: I think the field of biopharmaceutics has benefited most from a greater understanding of the fundamental role of solubility in oral bioavailability. This has continued to evolve to encompass the projected clinical dose of the NCE.

The Developability Classification System (DCS) by Butler and Dressman [5] allows the modelling of candidate molecules based on bio-relevant solubility e.g. FaSSIF/FASTFISH (fed state/fast state simulated intestinal solubility), permeability and clinical dose. Importantly, the DCS model allows for an assessment of the formulation strategies that can be employed to optimize oral bioavailability; particularly by comparison with formulations utilized by reference marketed compounds in the same DCS-space.

9. Without mentioning specific brand names, what are the most effective methods and tools for measuring solubility and providing for comprehensive solubility analysis?

ST: As with any area of science, the experience and discipline of the scientist is far more important than the methods and tools employed.

VB: Many analytical instrument companies have developed interesting approaches for the solubility measurement. I recently noticed that there is a unique and efficient approach called Cheqsol. In contrast to traditional techniques, it does not wait passively for equilibrium to be established. The point of equilibrium is actively sought by changing the concentration of the neutral form via a change in pH. Intrinsic solubility of weak acids, bases, and ampholytes is established. It drastically reduces the time required for an individual assay.

10. How useful is computational simulation, or “in-silico modeling,” to solubility prediction and analysis?

ST: This is an area that will see further growth over the coming years. Computational modeling will enable scientists to make connections that were never apparent before, providing they are not overwhelmed by the shear volume of data.

VB: While there is no substitute for laboratory data, solubility prediction can help compound screening at the discovery stage, as well as significantly increase the efficiency of formulation design. For example, solubility parameters are often used to predict the solubility of API in polymer. Especially in complex systems, solubility prediction could be extremely challenging. In some cases, it has proved a useful tool but there are also examples where it has been less successful in selecting the optimum polymer system. The industry needs more improvement and validation work on in-silico modeling and the prediction tools. Ultimately, these approaches will make the pharmaceutical research and development more efficient and productive.

References